

Original Article

Reduced graft function (with or without dialysis) vs immediate graft function—a comparison of long-term renal allograft survival

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Abstract

Background. Delayed graft function (DGF) is a common complication in cadaveric kidney transplants affecting graft outcome. However, the incidence of DGF differs widely between centres as its definition is very variable. The purpose of this study was to define a parameter for DGF and immediate graft function (IGF) and to compare the graft outcome between these groups at our centre.

Methods. The renal allograft function of 972 first cadaveric transplants performed between 1990 and 2001 in the Republic of Ireland was examined. The DGF and IGF were defined by a creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of <70 and >70%, respectively. Recipients with reduced graft function (DGF) not requiring dialysis were defined as slow graft function (SGF) patients. The serum creatinine at 3 months, 6 months, 1, 2 and 5 years after transplantation was compared between these groups of recipients. The graft survival rates at 1, 3 and 5 years and the graft half-life for DGF, SGF and IGF recipients were also assessed.

Results. Of the 972 renal transplant recipients, DGF was seen in 102 (10.5%) patients, SGF in 202 (20.8%) recipients and IGF in 668 (68.7%) patients. Serum creatinine levels were significantly different between the three groups at 3 and 6 months, 1, 2 and 5 years. Graft survival at 5 years for the DGF patients was 48.5%, 60.5% for SGF recipients and 75% for IGF patients with graft half-life of 4.9, 8.7 and 10.5 years, respectively.

Conclusion. This study has shown that the CRR at day 7 correlates with renal function up to 5 years post-transplantation and with long-term graft survival. We have also demonstrated that amongst patients with reduced graft function after transplantation, two groups with significantly different outcomes exist.

Keywords: delayed graft function; graft outcome; kidney transplantation

Introduction

Delayed graft function (DGF) is a common complication affecting renal grafts immediately post-transplantation. The definition of DGF, however, is arbitrary. The requirement for dialysis within the first week after renal transplantation is the most common definition [1,2]. Others have defined DGF as a GFR ≤ 10 ml/min 6 days post-transplantation, with or without dialysis [3] or a decrease in serum creatinine $\leq 10\%$ per day for the first week post-transplantation [4]. If the standard definition of DGF is accepted (i.e. the requirement of dialysis within the first week post-transplantation), there is still a substantial number of recipients with kidney graft dysfunction post-transplantation not requiring dialysis. These recipients do not, by standard definitions have DGF. However, the clinical course of these patients is not as smooth as those recipients who have immediate graft function (IGF). This group of patients have what has been defined as intermediate or slow graft function (SGF) [5].

The DGF takes its toll on graft outcome, although controversy exists regarding the long-term impact of DGF on the long-term renal graft survival. Some studies have shown a detrimental effect [6,7], whereas others have argued that in the absence of acute rejection, DGF has no long-term impact [8].

Significant recipient and donor risk factors linked to the development of DGF have been outlined by Ojo *et al.* [1], based on data from the US Scientific Renal Transplant Registry. A prolonged cold ischaemic time (CIT) showed a particularly strong association with DGF.

The incidence of DGF is variable amongst different centres and depending on how it is defined. According to

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data from the United Network for Organ Sharing (UNOS) in the US, the current incidence of DGF is 23% [9], but is about 30% in some centres in Europe [10]. However, the incidence of SGF is not frequently highlighted. The purpose of this study is to establish criteria where SGF could be defined as a distinct group and to examine graft outcomes, both short- and long-term, for the three groups (DGF, SGF and IGF). By establishing SGF as a distinct group, a particular subset of patients at increased risk of graft failure can be identified.

Subjects and methods

Data for our study was taken from the Irish Renal Transplant Registry. This registry includes details from all renal transplants carried out in the Republic of Ireland since 1964. The patient information is regularly updated to determine current graft function, graft loss or patient death.

In this retrospective study, the renal allograft function of 972 first cadaveric transplants carried out between 1990 and 2001 in the Republic of Ireland was examined. For the purposes of the study, DGF was defined as a creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of $\leq 70\%$ requiring dialysis (DGF) or without dialysis (SGF). Recipients with a CRR between time 0 of transplantation and day 7 post-transplantation of $\geq 70\%$ had IGF.

The 'classical' definition of DGF is the requirement for dialysis within the first week after renal transplantation [1,2]. In this study, we also wanted to examine that group of patients who did not require dialysis within the first week after transplantation, but did not have immediate graft function (SGF group). In a study by Boom *et al.* [4], DGF was defined as a serum creatinine which increased, remained the same or decreased $<10\%$ per day on three consecutive days post-transplantation. The use of CRR has been used previously by Rodrigo *et al.* [11], where DGF was defined as a CRR $\leq 30\%$ on day 2 post-transplantation. Taking all this into consideration, the definition we use for DGF and SGF (CRR at day 7 post-transplantation of $\leq 70\%$ with or without dialysis, respectively) incorporates all these definitions. Therefore, by day 7 post-transplantation, the decrease in CRR would be expected to be $\leq 70\%$ in the DGF patients.

The median serum creatinine for IGF, SGF and DGF was plotted over time and the serum creatinine at 3 and 6 months, 1, 2 and 5 years after transplantation was compared between DGF, SGF and IGF groups. Results between groups were compared using Kruskal–Wallis tests.

Pearson Chi-square tests and rank-scored methods were used to compare differences in the demographic table depending on whether analysis was for categorical or continuous variables. Ordered logistic regression was used to determine independently significant variables for predicting DGF.

The immunosuppression protocol varied during the study period. At our centre, cadaveric kidney transplant patients during the study period between 1990 and 2001 received a combination of a calcineurin inhibitor drug [cyclosporine 93% (907) or tacrolimus 6% (56)], steroids and either azathioprine [93% (905)] or mycophenolate mofetil [3% (30)] as induction immunosuppression treatment.

Patients received the combination of cyclosporine (initial dose 3 mg/kg), steroids and azathioprine or tacrolimus (initial dose 0.15 mg/kg), steroids and mycophenolate mofetil which started on the day of transplantation. Only 1% [9] of patients were treated with sirolimus in combination with cyclosporine as the calcineurin inhibitor therapy. No patient in the study received OKT3 or polyclonal antithymocyte globulins.

The graft survival at 1, 3 and 5 years for DGF, SGF and IGF recipients and the graft half-life were calculated. The Kaplan–Meier survivor functions were used to estimate survival probabilities at different time periods and comparisons were made using log-rank tests.

Risk analysis for graft loss using DGF and other relevant variables was measured using Cox proportional hazard models. Multi-factorial models were developed to analyse the independence of the effect of DGF, SGF and other parameters in the presence of various confounding variables.

Results

Of the 972 recipients of first cadaveric transplants in the study, 304 (31.28%) had reduced graft function (with or without dialysis) and 668 (68.72%) had IGF, according to the above definitions. Within the reduced graft function group, 102 patients (10.5%) required dialysis within the first week post-transplantation, which we defined as the DGF group, and 202 recipients (20.8%) had reduced graft function not requiring dialysis and so are defined as the SGF group.

Demographic characteristics of the three graft function groups are presented in Table 1. Variables that show significant differences between the study groups are highlighted. There is a notable older recipient and donor age and longer CIT in the SGF and DGF groups compared with the IGF group. An ordered logistic regression model with the above factors combined to test for independence of effect demonstrated that the donor age and CIT retained significance independently of other confounding factors ($P < 0.0001$) in predicting adverse graft function.

A significant difference in the acute rejection rates was detected between the three groups ($P = 0.012$). Rejection rates of 14.2, 16.2 and 26.5% for IGF, SGF and DGF, respectively, demonstrated substantially worse outcomes for the DGF group.

A substantial decline in serum creatinine was seen in the IGF group within the first 24–48 h post-transplantation. However, DGF and SGF recipients experienced a more gradual decline in their serum creatinine. The three groups plus the combined serum creatinine of the IGF, SGF and DGF groups were plotted over a 2-week period. This revealed stabilization in serum creatinine for the combined patient groups by day 7 post-transplantation (Figure 1). This is the primary reason why day 7 was used in our definition of DGF.

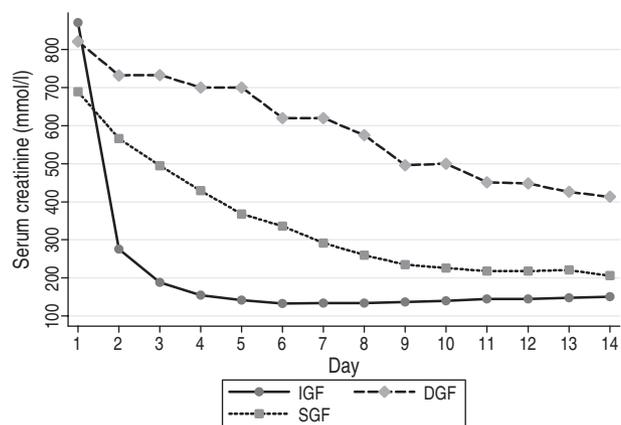
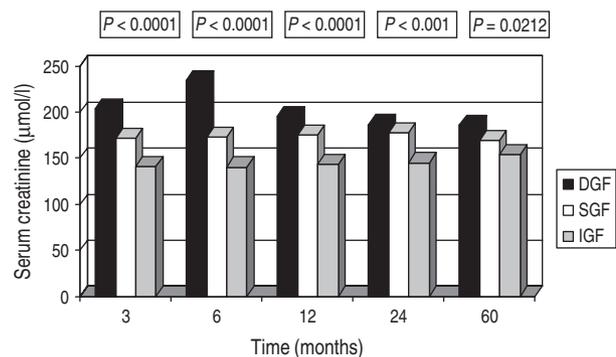
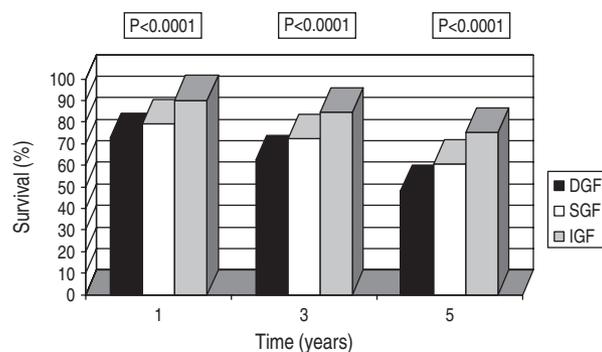
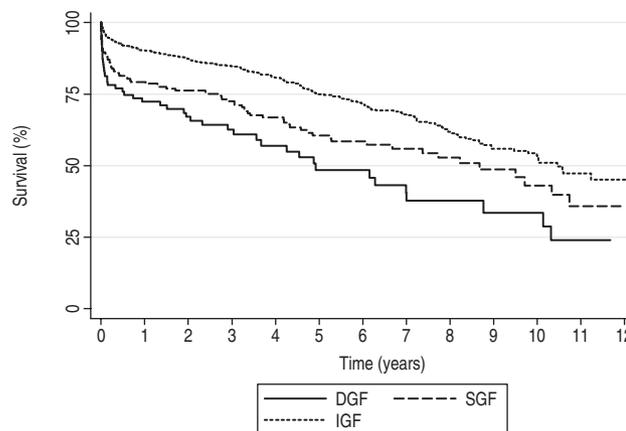
Subsequent follow-up of the serum creatinine at 3 and 6 months, 1, 2 and 5 years demonstrated significantly higher creatinines between the three groups (Figure 2). When the results were compared

Table 1. Demographical details of study groups

Variable	IGF	SGF	DGF	P-value
Age in years (mean SD)	39.99 (15.65)	43.93 (15.78)	45.19 (15.29)	<0.001
Donor age in years (mean SD)	32.28 (15.16)	38.70 (15.73)	41.35 (15.45)	<0.001
Gender (% M/F)	65/35	61/39	64/36	0.595
Donor gender (% M/F)	62/38	55/45	50/50	0.078
PRA group (% low/medium/high antibodies*)	87/10/3	82/13/5	80/18/2	0.086
Well-matched kidney (% well-matched/others**)	12/88	15/85	10/90	0.44
CIT (mean SD)	21.72 (6.03)	23.22 (6.65)	25.24 (7.20)	<0.001

Bold values indicate statistical significance.

*Low PRA (panel related antibody): PRA < 20; medium PRA, 20–80; high PRA, PRA ≥ 80. **Well-matched kidneys, number of mismatches = 000, 100 or 010. CIT, cold ischaemic time; SD, standard deviation.

**Fig. 1.** Decline in serum creatinine in the first 14 days post-transplantation.**Fig. 2.** Serum creatinine at various time points post-transplantation.**Fig. 3.** Graft survival at 1, 3 and 5 years between DGF, SGF and IGF recipients.**Fig. 4.** Kaplan-Meier survival curve for graft outcome.

between individual groups, there was a significantly higher serum creatinine observed in SGF recipients compared with the IGF patients at 3 and 6 months, 1 and 2 years ($P < 0.0001$), but not at 5 years ($P = 0.0746$). The serum creatinine was significantly lower in the SGF group compared with the DGF group at 3 and 6 months ($P = 0.0037$ and 0.0467 , respectively), but not at the later time points examined.

Graft survival outcomes are presented in Figures 3 and 4. Significantly lower survival percentages are evident in the DGF and SGF groups compared with the IGF patients at 1, 3 and 5 years. Graft survival at

1, 3 and 5 years was 72.4, 62.6 and 48.5%, respectively, for the DGF recipients, 79.2, 72.5 and 60.5%, respectively, for the SGF patients, and 90.2, 84.7 and 75.0%, respectively, for the IGF recipients (Figure 3).

Tests for graft survivor outcomes showed significant differences between the DGF, SGF and IGF groups ($P < 0.0001$). When analysed separately, there was a notable and significant difference in graft survival between the DGF and SGF patients ($P = 0.0487$), as was the graft survival outcome between SGF and IGF recipients ($P = 0.0002$). Graft half-lives of 4.9, 8.7 and 10.5 years for DGF, SGF and IGF recipients,

Table 2. Multifactorial model of variables that may influence graft survival

Variable	Hazard ratio	Standard error	P-value	95% Confidence interval
IGF–SGF–DGF	1.294	0.117	0.005	1.093–1.546
Acute rejection	5.289	0.783	<0.001	3.957–7.068
Recipient age	1.009	0.005	0.047	1.000–1.017
Recipient gender	0.961	0.128	0.766	0.741–1.247
Donor age	1.013	0.004	0.002	1.005–1.022
Donor gender	0.979	0.062	0.744	0.864–1.109
CIT	1.001	0.098	0.874	0.982–1.021
HLA (well-matched kidneys)	0.976	0.174	0.895	0.688–1.385
PRA group	1.260	0.147	0.049	1.001–1.585

Bold values indicate statistical significance.
 *HLA: human major histocompatibility complex.

respectively, can be deduced from the Kaplan–Meier survival curves (Figure 4).

From the various immunosuppression protocols described earlier, the combination of cyclosporine, steroids and azathioprine was received by 90% of the IGF patients, 88% SGF patients and 88% of the DGF patients. Tacrolimus, steroids and mycophenolate mofetil was used as immunosuppression for 2, 3 and 3% of IGF, SGF and DGF patients, respectively. There was no significant difference in the number of patients on one particular protocol between the study groups. The immunosuppressant regimen used by patients in the study had no effect on the graft outcome between the three study groups.

The effect of DGF and SGF on graft outcome was assessed using two multifactorial models (Tables 2 and 3), the purpose of which was to test for the independence of effect of these variables in the presence of confounding variables. The first model (Table 2) examined graft function as an independent variable in sequence of IGF, SGF and DGF. The second model excluded DGF and compared SGF with IGF in the presence of confounding variables. In both the models, the graft function itself, the occurrence of an acute rejection episode, older donor and recipient age and high PRA had a negative effect on graft survival.

Discussion

In this retrospective study, we examined the prognostic significance of poor graft function immediately after renal transplantation. In contrast to many other studies, a broader definition of reduced graft function (a creatinine reduction ratio between time 0 of transplantation and day 7 post-transplantation of $\leq 70\%$) was used. However, the group of patients with reduced initial function and not requiring dialysis after transplantation has been overlooked somewhat in the past (identified as SGF patients in our study).

Studies have used various time points and criteria in their definition of reduced graft function post-transplantation [4,11]. Day 7 after transplantation was used in our study to define graft function groups

Table 3. Multifactorial model of variables that may influence graft survival excluding DGF

Variable	Hazard Ratio	Standard error	P-value	95% Confidence interval
SGF	1.419	0.213	0.020	1.057–1.905
Acute rejection	6.802	1.066	<0.001	5.003–9.248
Recipient age	1.013	0.005	0.006	1.003–1.023
Recipient gender	0.943	0.133	0.677	0.715–1.243
Donor age	1.013	0.005	0.008	1.003–1.022
Donor gender	0.938	0.065	0.353	0.820–1.074
CIT	1.003	0.011	0.780	0.982–1.024
HLA (well-matched kidneys)	0.991	0.052	0.865	0.895–1.098
PRA group	1.335	0.168	0.022	1.043–1.707

Bold values indicate statistical significance.

largely because, we found that this time point coincided with the majority of patients achieving baseline levels of serum creatinine (Figure 1). In a study by Rodrigo *et al.* [11], DGF and SGF were defined as a CRR $\leq 30\%$ with or without dialysis, respectively, on day 2 post-transplantation. In both groups, the graft function was similar 1 week after transplantation. However, this was a very early time point to define the study groups. Boom *et al.* [4] defined DGF when the serum creatinine remained unchanged, increased or decreased $<10\%$ per day on three consecutive days in the first week post-transplantation. We choose day 7 post-transplantation as the time point in our definition as it combines the ‘classical’ definition of DGF (requirement for dialysis within 7 days post-transplantation) and the concept of an average CRR each day post-transplantation of ≤ 10 or $\geq 10\%$ to form a broader definition of a CRR on day 7 post-transplantation of ≤ 70 or $\geq 70\%$ with or without dialysis for the DGF, SGF and IGF groups, respectively.

One of the possible mechanisms of reduced graft function is the ischaemic damage to the graft before or during harvesting, and is further aggravated by the reperfusion syndrome, a multifactorial event in which polymorphonuclear cells are major components [12]. However, a spectrum of injury can occur from a subtle decrease in the expected decline in creatinine to the most severe form of injury, namely, DGF that requires dialysis. We have shown in this study that less severe injury (as in SGF recipients) also has a negative influence on graft outcomes.

Comparing demographic characteristics between the study groups, significantly older donor and recipient ages in the SGF and DGF groups as well as a longer CIT are evident. These factors provide evidence as to why patients are susceptible of being in one of the three groups. The logistic regression model suggests that donor age and CIT are the most important factors in determining poor graft function post-transplantation. Other centres have also shown that longer CIT has an influence on graft survival [1,4,10].

Rodrigo *et al.* [13] demonstrated no difference in the acute rejection rate between SGF and DGF patients, despite a difference between the IGF group and both

the SGF and DGF groups. However, in our study, we have shown a significant difference in the acute rejection rate between IGF, SGF and DGF patients ($P=0.012$).

There are conflicting reports from previous studies on graft survival in patients with SGF compared with those with DGF. Rodrigo *et al.* [13] showed a superior graft survival in IGF patients compared with SGF or DGF patients, but there was no significant difference in graft survival between the SGF and DGF groups. In their study, patients requiring dialysis within the first week of transplantation were described as having DGF, and IGF was differentiated from SGF according to whether day 5 serum creatinine was <3 or >3 mg/dl. However, when the same definitions of IGF, SGF and DGF were used in a study by Humar *et al.* [14], a similar greater graft outcome was found for IGF patients compared with the SGF or DGF patients, but there was a significantly worse graft outcome in the DGF group compared with the SGF group. In another study by Rodrigo *et al.* [11], DGF and SGF were defined as a CRR $\leq 30\%$ with or without dialysis, respectively, on day 2 post-transplantation. The graft function was worse in the DGF group compared with the SGF group only during the first week post-transplantation, but graft function was similar in both groups after this time point. However, when a comparison is made between graft survival of IGF, SGF and DGF in our study, we have demonstrated a 5-year graft survival of 75.1, 60.5 and 48.5% in the IGF, SGF and DGF groups, respectively, with a notable and significant difference in graft survival between the IGF and SGF groups ($P=0.002$) and between the SGF and DGF groups ($P=0.048$). The results of our study therefore argue strongly the graft survival disadvantage of both DGF compared to SGF, and SGF compared to IGF (Figure 4).

Multifactorial models examining DGF and SGF show these variables to be independent risk factors for graft loss. In particular, we have identified that both an acute rejection episode and graft function are independently significant predictors of graft outcome. Ojo *et al.* [1] also showed that both acute rejection and DGF independently, negatively predicted graft survival. However, we have shown in our study that, in addition to DGF and acute rejection, SGF also independently predicts a poor graft outcome.

In conclusion, it is important to acknowledge the whole spectrum of renal dysfunction after renal transplantation, and not solely DGF (the extreme dysfunction), as we have shown in this analysis that even a small compromise to the initial graft

performance can have a severe influence to short- and long-term outcomes.

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Conflict of interest statement. None declared.

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